SAMe-TT2R2 Score, Time in Therapeutic Range, and Outcomes in Anticoagulated Patients with Atrial Fibrillation

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Original article

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Running heading: SAME-TT_2R_2 score for anticoagulation control

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COMPETING INTERESTS

All authors - none specifically relevant to this manuscript.

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Author contributions

GYHL – original idea, supervised the research and drafted the paper.
VR, FM – supervised the research and drafted the paper.
PG - wrote the 1st draft and made
All authors had a role in drafting and writing the manuscript.

ABSTRACT

Background Oral anticoagulation is highly effective preventing stroke and mortality in non-valvular atrial fibrillation patients. However, the efficacy and safety of vitamin K antagonists, the main oral anticoagulation drug used) strongly depends upon the quantity of anticoagulation control, as reflected by the average percentage of the time in therapeutic range of INR (International Normalised Ratio) 2.0-3.0. An easy, simple prediction of which atrial fibrillation patients are likely to do well on vitamin K antagonists (with good average time in therapeutic range) could guide decision-making between using vitamin K antagonists (eg. warfarin) and non-vitamin K antagonist oral anticoagulants (NOACs).

Methods and Results In a consecutive cohort of non-valvular atrial fibrillation patients attending our anticoagulation clinic, we tested the hypothesis that the new SAME-TT_2R_2 score was a predictor for good average time in therapeutic range, and second, this would translate into adverse events in a 'real world' cohort of patients with non-valvular atrial fibrillation.

The incidence of both bleeding, adverse cardiovascular events (including stroke/thromboembolism) and mortality during the follow-up was higher with increasing SAME-TT_2R_2 score. The SAME-TT_2R_2 score was predictive for the composite of all adverse events [Hazard Ratio: 1.32 (1.17-1.50); p<0.001], adverse cardiovascular events [1.52 (1.28-1.83); p<0.001], and all-cause mortality [1.41 (1.16-1.67); p=0.001]. A trend was also observed for major bleeding events [1.23 (0.99-1.53); p=0.059].

Conclusion In a 'real world' cohort of consecutive patients with non-valvular atrial fibrillation, a high SAME-TT_2R_2 score (reflecting poor anticoagulation control with poor time in therapeutic range) was associated with more bleeding, adverse cardiovascular events and mortality during follow-up.

Key words: SAME-TT_2R_2 score, atrial fibrillation, anticoagulation, stroke, bleeding, mortality

INTRODUCTION

Oral anticoagulation is highly effective preventing stroke and mortality in non-valvular atrial fibrillation patients[1]. However, the efficacy and safety of vitamin K antagonists depends upon the quality of anticoagulant control, as reflected by the average percentage of the time in therapeutic range of INR 2.0-3.0. Various studies have shown how a high time in therapeutic range translates into a lower risk of stroke and bleeding, whilst on oral anticoagulation [2-4]. A recent European consensus document recommends that an average individual time in therapeutic range should be >70% for optimal efficacy and safety outcomes whilst on a vitamin K antagonists and this is also recommended in international guidelines [5]. The vitamin K antagonists were the main oral anticoagulant drug used until the introduction of the non-vitamin K antagonist oral anticoagulants (NOACs, previously referred to as novel or new oral anticoagulants).

The difficulties in achieving a high time in therapeutic range as well as the inconvenience of regular anticoagulation monitoring and the various food/drug restrictions associated with the vitamin K antagonists have led to the recent introduction of the NOACs, which offer improved efficacy, safety and convenience compared to the vitamin K antagonists [5]. Even in clinical trials, patients in centres with high average time in therapeutic range have less marked difference in efficacy outcomes between NOACs and warfarin [6].

An easy, simple prediction of which atrial fibrillation patients are likely to do well on vitamin K antagonists (with good average time in therapeutic range) could guide decision-making between using vitamin K antagonists and NOACs. Recently,

Apostolakis et al [7] proposed and validated the SAME-TT_2R_2 score [**S**ex, **A**ge (<60 years), **Me**dical history (at least 2 of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease), Treatment (interacting drugs eg amiodarone for rhythm control) [all 1 point], as well as current **T**obacco use (2 points) and **R**ace (non-Caucasian; 2 points)] (see Table 1).This simple score (SAMe-TT_2R_2) could help decision making by identifying those atrial fibrillation patients that would do well on vitamin K antagonists (with a high average time in therapeutic range, with SAMe-TT_2R_2 score=0-1), or conversely, those likely to have anticoagulation control (ie. poor average time in therapeutic range, with SAMe-TT_2R_2 score ≥2) who require additional interventions to achieve acceptable anticoagulation control or be candidates for NOACs. This score was derived from the AFFIRM (Atrial Fibrillation Followup Investigation of Rhythm Management) trial population and externally validated in a small 'real world' cohort of anticoagulated non-valvular atrial fibrillation patients[7]. Further validations in large 'real world' cohorts are necessary, also to assess whether this score (which reflects time in therapeutic range) translates into adverse outcomes in anticoagulated non-valvular atrial fibrillation patients.

In a consecutive cohort of non-valvular atrial fibrillation patients attending our anticoagulation clinic, we tested the hypothesis that new SAME-TT_2R_2 score as a predictor for average time in therapeutic range. Second, we investigated whether the latter translated into adverse events (major bleeding, adverse cardiovascular

events, mortality) in our 'real world' cohort of patients with non-valvular atrial fibrillation.

METHODS

We recruited consecutive patients with permanent or paroxysmal atrial fibrillation on a vitamin K antagonist from our outpatient anticoagulation clinic. In order to homogenize the baseline cohort of patients, only patients who had an International Normalised Ratio between 2.0 and 3.0 during the previous 6 months were included. Patients with prosthetic heart valves or valvular atrial fibrillation were excluded from the study, as well as those presenting acute coronary syndrome, stroke (ischaemic or embolic), any haemodynamic instability or hospital admission or surgical intervention in the preceding 6 months. A history of malignancy was allowed if the patient's expected survival duration was more than 6 months and not receiving chemotherapy or radiotherapy at study entry. A complete medical history was recorded at inclusion. Follow-up was performed through visits to the anticoagulation clinic, the hospital electronic medical records system or, when unavailable or persisting doubts, by telephone interview.

Baseline stroke risk was assessed using the CHA_2DS_2-VASc [Cardiac failure or dysfunction, Hypertension, Age over 75 years [Doubled], Diabetes, Stroke [Doubled] – Vascular disease, Age between 65-74 and Sex category [Female]) score, as described in recent guidelines [5;8]. The HAS-BLED bleeding risk score was calculated as a measure of baseline bleeding risk, as the result of adding one point to Hypertension, Abnormal

renal/liver function (one point each), Stroke, Bleeding history or predisposition, Labile International Normalised Ratio(INR), Elderly (age over 65) and Drugs/alcohol concomitantly (one point for each one) [9].

Adverse cardiovascular end-points (mainly thromboembolic) were defined as stroke/transient ischemic attack, peripheral embolism, acute coronary syndrome, acute heart failure and cardiac death. Bleeding events were assessed by the 2005 International Society on Thrombosis and Haemostasis (ISTH) criteria, including fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells[10]. Finally, we recorded all-cause mortality, and whether the cause of death was secondary to a cardiovascular event (stroke/ transient ischemic attack, peripheral embolism, acute coronary syndrome, acute heart failure and cardiac death) or a haemorrhagic one. At six months after inclusion, we calculated the percentage of International Normalised Ratio measures within the therapeutic range during the previous 6 months, as an estimation of the time in therapeutic range.

The protocol study was approved by the Ethical Committee from University Hospital Morales Meseguer, and patients gave informed consent to participation in the study.

Statistical analysis

Continuous variables were tested for normality by the Kolmogorov-Smirnov test. Continuous variables are presented as a mean ± standard deviation (SD) or median (interquartile range, IQR), as appropriate, and categorical variables as a percentage.

Cox models were used to determine the association between clinical risk factors and bleeding, as well as cardiovascular events and mortality. The independent effect of clinical variables on prognosis was calculated using a Cox proportional hazard regression model, and analysis of variance (ANOVA) models were used to compare means between different groups. The c-statistic was calculated using ROC curves. A $p<0.05$ was accepted as statistically significant. Statistical analyses were performed using SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL, USA).

RESULTS

We studied 972 patients (49% male, median age 76 years [interquartile range (IQR) 70-80] [Table 2]. The median CHA_2DS_2-VASc score was 4 (IQR 3-5) and 93% had a CHA_2DS_2-VASc score ≥2. The median HAS-BLED score was 2 (IQR 2-3).

Median follow-up was 952 (784-1078) days, and during this period, 107 patients had an adverse cardiovascular event (4.22%/year): of these35 were strokes (1.38%/year), 42 were acute coronary syndrome events (1.65%/year) and 31 acute heart failure events (1.22%/year). Of the cohort, 77 patients presented with a major bleeding (3.04%/year) and 91 patients died (3.59%/year). In the following 6 months after inclusion, mean time in therapeutic range was 78.0±19.98%.

Predictive value for anticoagulation control

In our anticoagulated patients, increasing baseline SAME-TT_2R_2 score was associated with significantly lower mean time in therapeutic range at 6 months after inclusion. This ranged from 79.7% for patients with SAME-TT_2R_2score of 0 points to 72.3% for patients with 5 points (p=0.043) [Table 3].

Predictive value of the SAME-TT_2R_2 score for bleeding, cardiovascular events and death

The SAME-TT_2R_2 score had a c-statistic for adverse cardiovascular events of 0.62 (95%CI 0.57-0.68; p<0.001); for bleeding, the c-statistic was 0.55 (95%CI 0.49-0.62; p=0.117). For all-cause mortality, the c-statistic was 0.62 (95%CI 0.55-0.68; p<0.001).

Major adverse events

The incidence of both adverse cardiovascular events (including stroke/ thromboembolism) and bleeding and mortality during the follow-up was higher with increasing SAME-TT_2R_2 score at baseline (Figure 1).

On unadjusted (crude) analyses, the SAME-TT_2R_2 score was predictive for the composite of all adverse events [Hazard Ratio, HR: 1.32 (1.17-1.50); p<0.001], adverse cardiovascular events [HR 1.52 (1.28-1.83); p<0.001], and for all-cause mortality [1.41(1.16-1.71); p=0.001]. Only a non-significant trend was seen regarding major bleeding events [1.23 (0.99-1.53); p=0.059].

Discussion

In a 'real world' cohort of consecutive patients with non-valvular atrial fibrillation, we have shown that a low SAME-TT_2R_2 score was a significant predictor for good anticoagulation control (as reflected by time in therapeutic range). A high SAME-TT_2R_2 score (reflecting poor anticoagulation control with poor time in therapeutic range) translated into more bleeding, adverse cardiovascular events (including stroke/thromboembolism) and mortality during follow-up. To the best of our knowledge, we have also validated the SAME-TT_2R_2 score for the first time in consecutive atrial fibrillation patients taking acenocoumarol treatment as their oral anticoagulant (rather than warfarin).

Non-valvular atrial fibrillation patients are at high risk for cardiovascular events and mortality. Our population was an elderly cohort with non-valvular atrial fibrillation where over 50% were aged>75 years. Moreover, our population had an intermediate-high thrombotic risk and multiple prevalent comorbidities. Even though patients with good drug compliance, various acute or clinical decompensate events may lead to unstable International Normalised Ratio control, and therefore, good prior International Normalised Ratio control does not necessarily imply good control in the future. Also, the largest randomised trial of genotype-guided (pharmacogenetically based) dosing of warfarin did not result in improved anticoagulation control [11]. Thus, the ability to have a simple, practical way to predict who is likely to do well on vitamin K antagonists, or those less likely to have good anticoagulation control where NOACs would benefit could help decision making in everyday clinical practice [12, 13].

International Normalised Ratio control and quality of anticoagulation is most often assessed by the time in therapeutic range. The average individual time in therapeutic range is known to increase over time, as more International Normalised Ratio fluctuations occur during the first 3 months following initiation of vitamin K antagonists [14]. Good adherence to the therapy, as well as minimising drug or diet interactions influences time in therapeutic range outcomes. In the present study, we selected experienced anticoagulated patients with excellent anticoagulation control at baseline to ensure some degree of patient homogeneity, and thus adherence to the therapy was expected to be high and not affect subsequent measurements. However, we found that the SAME-TT_2R_2 score was still able to predict which patients were prone to subsequent instability and poor International Normalised Ratio control, even among previously anticoagulated patients, with good time in therapeutic range at inclusion. Slight differences were observed, among the different range of SAME-TT_2R_2 scores, due to our inclusion criteria, given that all patients had shown previously excellent International Normalised Ratio control.

The SAME-TT_2R_2 score was found to be predictive for both adverse cardiovascular events and mortality, but only a trend was observed regarding major bleeding events. It should be beard in mind that the anticoagulation control in our cohort was optimal and therefore only few major bleeding events occurred during the follow-up (with a rate of 3%/year).

Although the SAME-TT_2R_2 score at baseline is related to outcomes (mainly adverse cardiovascular events and mortality, but also to major bleeding), the low c-statistics show a moderate discriminatory ability of the survival model. This might be related to

low outcome event rates (manly few major bleeding events during the follow-up, with an annual rate of 3%/year), due to the good control of anticoagulation therapy in our (selected) cohort at baseline. Given the modest discriminatory ability (as reflected by c-statistics) of the SAME-TT_2R_2 score in our well controlled anticoagulated clinic population, it is unclear how the score would perform in a less meticulously cared for group of patients.

Of note, we studied a Caucasian population, without any prevalence of other ethnic races, which is one of the risk factors for poor time in therapeutic range, based on the SAME-TT_2R_2 score [7]. Thus, none of the patients could reach a SAME-TT_2R_2 score of >6 points. Moreover, high scores were poorly represented in our cohort, as only 6 patients had a score of 5 and none has a score of 6, perhaps reflecting our selection criteria, as stable International Normalised Ratio was required at baseline. Indeed, patients with the highest SAME-TT_2R_2scores did not achieve good anticoagulation control and therefore were probably excluded from the present cohort.

Limitations

The possibility of some selection bias cannot be excluded as our patients were clinically stable at stable entry, so unstable patients who are more prone to have adverse events were excluded, unlike other clinical studies where patients recruited would present with a time in therapeutic range ranging from 60 to 75%. Similarly, we selected for our cohort 'anticoagulation experienced' patients with proven adherence and good anticoagulation control during 6 months prior to inclusion. Thus, patients with erratic anticoagulation (who would probably have higher SAME-TT_2R_2score values) were excluded from the analysis. This specific selection of patients (stable on

acenocumarol with high initial time in therapeutic range at entry) would perhaps limit the generalizability of our findings to less well-controlled populations. Furthermore, we used acenocoumarol (the most widely used vitamin K antagonists in Spain), which differs from the warfarin with a shorter half-life, which is perceived to lead to more unstable anticoagulation, although no results comparing the different vitamin K antagonists have been published. We also presumed that patients with high SAME-TT_2R_2 score would be "suitable" to be treated with NOAC, but we have not studied such a population. Finally, we studied a Caucasian population, without any other races being studied, and thus, further studies in ethnically diverse populations would be required. Ongoing prospective studies will address all these aspects.

In conclusion, a low SAME-TT_2R_2 score was a significant predictor for a good anticoagulation control (as reflected by time in therapeutic range), whilst a high SAME-TT_2R_2 score (reflecting poor anticoagulation control) was associated with more bleeding, adverse cardiovascular events and mortality during follow-up. Thus, the simple SAME-TT_2R_2 score may aid decision-making by identifying those atrial fibrillation patients likely to do well on Vitamin K antagonist (score 0-2) or those likely to have poor(er) anticoagulation control (score >2) who could be better off being started on NOACs as initial therapy, or be 'flagged up' for more aggressive efforts to improve anticoagulation control.

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Table 1. The SAME-TT_2R_2 score

S	**S**ex (female)	1
A	**A**ge (less than 60 years)	1
M **e**	**Me**dical history[1]	1
T	**T**reatment (rhythm control strategy)	1
T	**T**obacco use (within 2 years)	2
R	**R**ace (non Caucasian)	2

[1]Defined as more than 2 of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease.

Table 2.Baseline clinical characteristics

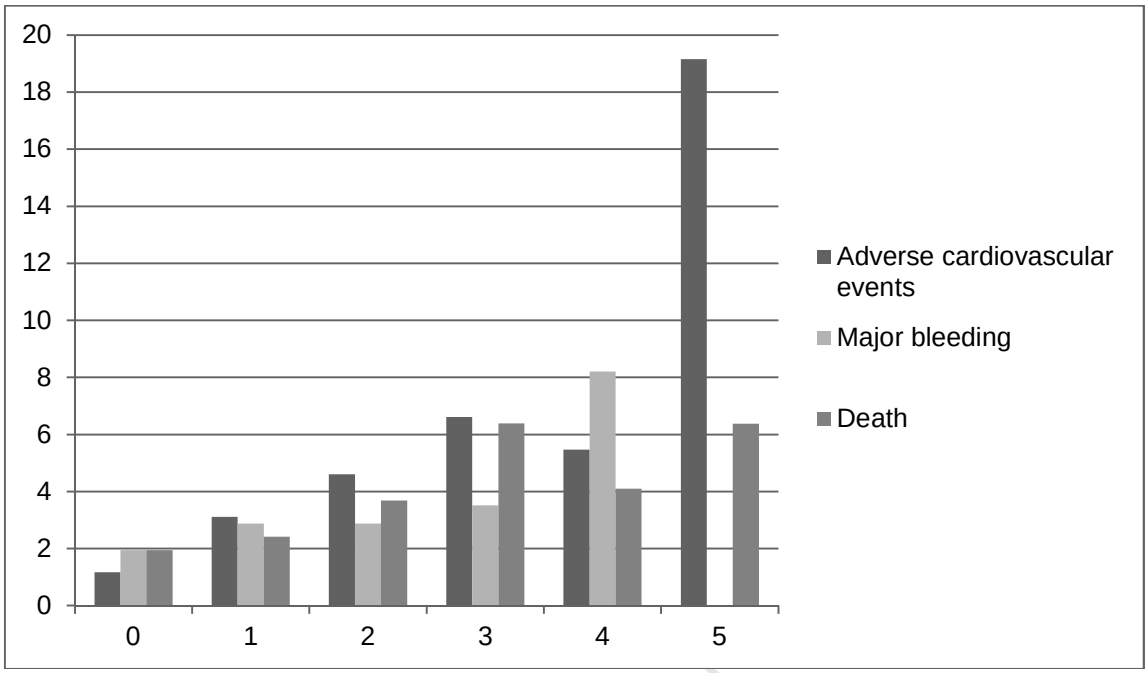
Baseline characteristics	N= 972
Male sex	478 (49%)
Age, median (IQR)	76 (70-80)
Age < 60	66 (7%)
Hypertension	796 (82%)
Diabetes mellitus	249 (26%)
Heart failure	350 (36%)
History of stroke or TIA	182 (19%)
Hepatic impairment	11 (1%)
Renal impairment	94 (10%)
Coronary artery disease	182 (19%)
Hypercholesterolemia	303 (31%)
Current smoking habit	136 (14%)
Current alcoholic consumption	24 (2.5%)
Previous bleeding episode	79 (8%)
Concomitant malignant disease	58 (6%)
Concomitant treatment	
Antiplatelet therapy	156 (16%)
Angiotensin-converting enzyme inhibitors	244 (25%)
Angiotensin-renin blockers	214 (22%)
Calcium antagonist	208 (21%)
Beta-blockers	293 (30%)
Statins	202 (21%)
Digoxin	179 (18%)
Diuretics	401 (41%)
CHA_2DS_2-VASc score, median (IQR)	4 (3-5)
HAS-BLED score, median (IQR)	2 (2-3)
SAME-TT_2R_2 score, median (IQR)	2 (1-2)

CHA_2DS_2-VASc: Cardiac failure or dysfunction, Hypertension, Age ≥75[Doubled], Diabetes, Stroke[Doubled] – Vascular disease, Age 65-74 and Sex category [Female]
HAS-BLED: Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly

Table 3.Baseline SAME-TT_2R_2

SAME-TT_2R_2 score	**score**	**TTR at 6 months follow-up** Mean (± standard deviation)	**N= 972**
• Low	**0 – 1**	79.67(± 19.46)	431 (44%)
• Borderline	**2**	78.40 (±20.28)	332 (34%)
• High	**≥3**	74.25 (±20.24)	208 (22%)

Figure 1. Adverse events according to SAME-TT_2R_2 score at baseline.



Clinical significance:

- In a 'real world' cohort of consecutive patients with NVAF, a high SAME-TT_2R_2 score (reflecting poor anticoagulation control with poor time-in-therapeutic range (TTR)) was associated with more bleeding, adverse cardiovascular events and mortality during follow-up.
- The SAME-TT_2R_2 score is an easy, simple prediction of which AF patients are likely to do well on VKA (with good average TTR) could guide decision-making between using VKAs and non-VKA oral anticoagulants (NOACs).